**Remarks**

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Claims 1-90 have been canceled without prejudice as being directed to non-elected subject matter. Applicant reserves the right to pursue the non-elected subject matter in one or more related cases. Claim 91 has been amended to better describe the claimed invention. Support for the amendment can be found in page 14, lines 21-26, page 15, lines 5-8, and page 82, lines 14-17 of the present application. Claims 1, 2, 5, 6, 13-20, 23-30, 33-40, 43-49, 115, 116, and 119-122 remain pending. In addition, applicant submits herewith the Declaration of Thomas A. Szyperski under 37 C.F.R. § 1.132 ("Szyperski Declaration") to discuss the references cited in the outstanding office action and to submit evidence of the unobviousness of the present invention.

The rejection of claims 91-102, 131, and 132 under 35 U.S.C. § 103(a) for obviousness over Szyperski et al., "Sequential Resonance Assignment of Medium-Sized $^{15}N/^{13}C$ -Labeled Proteins with Projected 4D Triple Resonance NMR Experiments," *J. Biomol. NMR* 11:387-405 (1998) ("Szyperski") in view of Fernández et al., "NMR With $^{13}C$, $^{15}N$ -Doubly-Labeled DNA: The *Antennapedia* Homeodomain Complex With a 14-mer DNA Duplex," *J. Biomol. NMR* 12:25-37 (1998) ("Fernández") or Gehring et al., "H(C)CH-COSY and (H)CCH-COSY Experiments for $^{13}C$-Labeled Proteins in $H_2O$ Solution," *J. Magn. Reson.* 135(1):185-193 (1998) ("Gehring") and Yamazaki et al., "Two-Dimensional NMR Experiments for Correlating $^{13}C\beta$ and $^{1}H$ $\delta/\varepsilon$ Chemical Shifts of Aromatic Residues in $^{13}C$-Labeled Proteins Via Scalar Couplings," *J. Am. Chem. Soc.*, 115:11054-11055 (1993) ("Yamazaki") is respectfully traversed. In addition, the rejection of claims 103-130 under 35 U.S.C. § 103(a) for obviousness over Szyperski in view of Fernández or Gehring and Yamazaki, as applied to claims 91-102 and 131-132 above, and further in view of Schirra, "Three Dimensional NMR Spectroscopy" http://www.cryst.bbk.ac.uk/PPS2/projects/schirra/html/3dnmr.htm (1996) ("Schirra") or "Cell Cycle/Gene Regulation," http://daisy.bio.nagoya-u.ac.jp/golab/pdb/pdb2nmb.txt (1998) ("Cell Cycle Protocol") is respectfully traversed.

Szyperski describes the use of projected four-dimensional (4D) triple resonance NMR experiments for the efficient sequential resonance assignment of $^{15}N/^{13}C$-labeled proteins, where a reduced dimensionality (RD) three-dimensional (3D)

$H^{\alpha/\beta}C^{\alpha/\beta}$(CO)NHN NMR experiment is recorded either in conjunction with a RD 3D HNN<CO,CA> NMR experiment or with a RD 3D HNNCAHA NMR experiment. As already acknowledged on page 3 of the outstanding office action, Szyperski does not in any way teach or suggest conducting a "RD 3D H,C,C,H-COSY NMR experiment" or a "RD two-dimensional (2D) HB,CB,(CG,CD),HD NMR experiment" as in claim 91.

Fernández discloses obtaining $^{1}H$, $^{13}C$, and $^{15}N$ NMR assignments for a doubly-labeled 14-base pair DNA duplex in solution, both in the free state and complexed with the uniformly $^{15}N$-labeled *Antennapedia* homeodomain. The resonance assignments are obtained in three steps: (i) identification of the deoxyribose spin systems via scalar couplings using 2D and 3D HCCH-COSY and soft-relayed HCCH-COSY; (ii) sequential assignment of the nucleotides via $^{1}H$-$^{1}H$ nuclear Overhauser effects (NOEs) observed in 3D $^{13}C$-resolved NOESY; and (iii) assignment of the immino and amino groups via $^{1}H$-$^{1}H$ NOEs and $^{15}N$-$^{1}H$ correlation spectroscopy. With respect to the present invention, Fernández discloses nothing more than conventional HCCH-COSY NMR experiments. It does not in any way disclose or suggest any reduced dimensionality (RD) NMR experiments, let alone a "RD 3D H,C,C,H-COSY NMR experiment", as in claim 91.

Gehring discloses three experiments for identifying carbon and proton sidechain resonances in $^{13}C$-labeled proteins. The first experiment is an improved H(C)CH-COSY experiment comprising the application of gradients for coherence selection and a reduction in the phase cycle. The second experiment is a new (H)CCH-COSY experiment with two carbon dimensions. The third experiment is a 2D proton-edited (H)C(C)H-COSY experiment that allows suppression of methylene resonances. Gehring discloses nothing more than conventional HCCH-COSY NMR experiments and does not in any way disclose or suggest any reduced dimensionality (RD) NMR experiments, let alone a "RD 3D H,C,C,H-COSY NMR experiment", as in claim 91.

Yamazaki discloses two-dimensional NMR experiments, (Hβ)Cβ(CγCδ)Hδ and (Hβ)Cβ(CγCδCε)Hε, for correlating $^{13}C\beta$ and $^{1}H$ δ/ε chemical shifts of aromatic residues in $^{13}C$-labeled proteins based on scalar connectivities. Yamazaki discloses nothing more than a conventional 2D (Hβ)Cβ(CγCδ)Hδ NMR experiment and does not in any way disclose or suggest any reduced dimensionality (RD) NMR experiments, let alone a "RD 2D HB,CB,(CG,CD),HD NMR experiment", as in claim 91.

Schirra discloses several 3D NMR experiments and their magnetization transfer pathways. Schirra discloses nothing more than conventional 3D NMR experiments

and does not in any way disclose or suggest any reduced dimensionality (RD) NMR experiments, let alone a specific RD 3D NMR experiment, as in claims 103-130.

Cell Cycle Protocol is a copy of a printout of a protein databank entry, listing a number of conventional multidimensional NMR experiments that were recorded. Cell Cycle Protocol discloses nothing more than conventional NMR experiments and does not in any way disclose or suggest any reduced dimensionality (RD) NMR experiments, let alone a specific RD 3D NMR experiment, as in claims 103-130.

There would have been no motivation to combine the subject matter of Szyperski, Fernández or Gehring, Yamazaki, Schirra, and Cell Cycle Protocol. None of the references provides the motivation for making the combination set forth in the outstanding office action nor is there any basis in the art itself. Contrary to the PTO's statement on page 4 of the outstanding office action, none of the experiments disclosed in Fernández, Gehring, Yamazaki, Schirra, or Cell Cycle Protocol creates the same conditions created by the RD NMR experiments disclosed in Szyperski, i.e., a cosine-modulation of the transfer amplitude, yielding peak doublets encoding n chemical shifts in a n-1 dimensional spectrum.

Thus, Szyperski, on pages 388-392 and in Figures 1-2, describes RD NMR experiments which involve a cosine-modulation of the transfer amplitude, yielding peak doublets encoding n chemical shifts in an n-1 dimensional spectrum, thereby encoding one of the n chemical shifts into the spectral separation of the two peaks (Szyperski Declaration ¶ 8).

Fernández describes conventional multidimensional NMR experiments, where the indirect chemical shift evolution times sample only a single chemical shift, as indicated by the radiofrequency pulse schemes (shown in Figure 2) used in these experiments (Szyperski Declaration ¶ 9). The conditions created in RD NMR, i.e., a cosine-modulation of the transfer amplitude, yielding peak doublets encoding n chemical shifts in a n-1 dimensional spectrum, can be achieved only if a second chemical shift is jointly sampled with the one being detected in quadrature (*Id.*). No such joint sampling is even implemented or suggested in Fernández (*Id.*). Thus, contrary to the statement in the outstanding office action, the conditions created by the conventional NMR experiments disclosed in Fernández are not the same conditions created by the RD NMR experiments disclosed in Szyperski (*Id.*). Accordingly, there can be no basis for modifying the experiments disclosed in Fernández to conduct a RD NMR experiment as taught by Szyperski (*Id.*). Moreover, it is not trivial to identify the best choice for two chemical shifts to be jointly sampled in order to conduct a RD NMR experiment, and Fernandez provides no information in that respect (*Id.*). Fernández

neither attempts to nor achieves the assignment of protein resonance by conducting any RD NMR experiments, let alone a RD 3D H,C,C,H-COSY NMR experiment (*Id.*). Furthermore, Fernández does not provide any expectation that conducting a RD NMR experiment would be useful in obtaining protein resonance assignments (*Id.*).

Gehring describes conventional multidimensional NMR experiments, where the indirect chemical shift evolution times sample only a single chemical shift, as indicated by the radiofrequency pulse schemes (shown in Figure 1) used in these experiments (Szyperski Declaration ¶ 10). The conditions created in RD NMR, i.e., a cosine-modulation of the transfer amplitude, yielding peak doublets encoding n chemical shifts in a n-1 dimensional spectrum, can be achieved only if a second chemical shift is jointly sampled with the one being detected in quadrature (*Id.*). No such joint sampling is even implemented or suggested in Gehring (*Id.*). Thus, contrary to the statement in the outstanding office action, the conditions created by the conventional NMR experiments disclosed in Gehring are not the same conditions created by the RD NMR experiments disclosed in Szyperski (*Id.*). Accordingly, there can be no basis for modifying the experiments disclosed in Gehring to conduct a RD NMR experiment as taught by Szyperski (*Id.*). Moreover, it is not trivial to identify the best choice for two chemical shifts to be jointly sampled in order to conduct a RD NMR experiment, and Gehring provides no information in that respect (*Id.*). Gehring neither attempts to nor achieves the assignment of protein resonance by conducting any RD NMR experiments, let alone a RD 3D H,C,C,H-COSY NMR experiment (*Id.*). Furthermore, Gehring does not provide any expectation that conducting a RD NMR experiment would be useful in obtaining protein resonance assignments (*Id.*).

Yamazaki describes conventional two-dimensional NMR experiments, where the indirect chemical shift evolution times sample only a single chemical shift, as indicated by the radiofrequency pulse schemes (shown in Figure 1) used in these experiments (Szyperski Declaration ¶ 11). The conditions created in RD NMR, i.e., a cosine-modulation of the transfer amplitude, yielding peak doublets encoding n chemical shifts in a n-1 dimensional spectrum, can be achieved only if a second chemical shift is jointly sampled with the one being detected in quadrature. No such joint sampling is even implemented or suggested in Yamazaki (*Id.*). Thus, contrary to the statement in the outstanding office action, the conditions created by the conventional NMR experiments disclosed in Yamazaki are not the same conditions created by the RD NMR experiments disclosed in Szyperski (*Id.*). Accordingly, there can be no basis for modifying the experiments disclosed in Yamazaki to

conduct a RD NMR experiment as taught by Szyperski (*Id.*). Moreover, it is not trivial to identify the best choice for two chemical shifts to be jointly sampled in order to conduct a RD NMR experiment, and Yamazaki provides no information in that respect (*Id.*). Yamazaki neither attempts to nor achieves the assignment of protein resonance by conducting any RD NMR experiments, let alone a RD RD 2D HB,CB,(CG,CD),HD NMR experiment (*Id.*). Furthermore, Yamazaki does not provide any expectation that conducting a RD NMR experiment would be useful in obtaining protein resonance assignments (*Id.*).

Schirra describes conventional multidimensional NMR experiments, where the indirect chemical shift evolution times sample only a single chemical shift (Szyperski Declaration ¶ 12). The conditions created in RD NMR, i.e., a cosine-modulation of the transfer amplitude, yielding peak doublets encoding n chemical shifts in a n-1 dimensional spectrum, can be achieved only if a second chemical shift is jointly sampled with the one being detected in quadrature (*Id.*). No such joint sampling is even implemented or suggested anywhere in Schirra (*Id.*). Thus, contrary to the statement in the outstanding office action, the conditions created by the conventional NMR experiments disclosed in Schirra are not the same conditions created by the RD NMR experiments disclosed in Szyperski (*Id.*). Accordingly, there can be no basis for modifying the experiments disclosed in Schirra to conduct a RD NMR experiment as taught by Szyperski (*Id.*). Moreover, it is not trivial to identify the best choice for two chemical shifts to be jointly sampled in order to conduct a RD NMR experiment, and Schirra provides absolutely no information in that respect (*Id.*). Schirra neither attempts to nor achieves the assignment of protein resonance by conducting any RD NMR experiments, let alone any RD 3D NMR experiment (*Id.*). Furthermore, Schirra does not provide any expectation that conducting a RD NMR experiment would be useful in obtaining protein resonance assignments (*Id.*).

Cell Cycle Protocol describes conventional multidimensional NMR experiments, where the indirect chemical shift evolution times sample only a single chemical shift (Szyperski Declaration ¶ 13). The conditions created in RD NMR, i.e., a cosine-modulation of the transfer amplitude, yielding peak doublets encoding n chemical shifts in a n-1 dimensional spectrum, can be achieved only if a second chemical shift is jointly sampled with the one being detected in quadrature (*Id.*). No such joint sampling is even implemented or suggested anywhere in Cell Cycle Protocol (*Id.*). Thus, the conditions created by the conventional NMR experiments disclosed in Cell Cycle Protocol are not the same conditions created by the RD NMR experiments disclosed in Szyperski (*Id.*). Accordingly, there can be

no basis for modifying the experiments disclosed in Schirra to conduct a RD NMR experiment as taught by Szyperski (*Id.*). Moreover, it is not trivial to identify the best choice for two chemical shifts to be jointly sampled in order to conduct a RD NMR experiment, and Cell Cycle Protocol provides absolutely no information in that respect (*Id.*). Cell Cycle Protocol neither attempts to nor achieves the assignment of protein resonance by conducting any RD NMR experiments, let alone any RD 3D or 2D NMR experiment (*Id.*). Furthermore, Cell Cycle Protocol does not provide any expectation that conducting a RD NMR experiment would be useful in obtaining protein resonance assignments (*Id.*).

Since none of the experiments disclosed in Fernández, Gehring, Yamazaki, Schirra, or Cell Cycle Protocol creates the same conditions created by the RD NMR experiments disclosed in Szyperski, i.e., a cosine-modulation of the transfer amplitude, yielding peak doublets encoding n chemical shifts in a n-1 dimensional spectrum, there can be no basis for combining the references as proposed by the outstanding office action. Therefore, in view of the absence of any motivation to combine the cited references, the rejection based upon them should be withdrawn.

Even if the references were combinable, which they are not, their combination would not teach the claimed invention. As noted above, Szyperski does not disclose or suggest conducting a "RD 3D H,C,C,H-COSY NMR experiment" or a "RD two-dimensional (2D) HB,CB,(CG,CD),HD NMR experiment" as in claim 91. None of the other cited references overcome this deficiency. Since the combination of Szyperski, Fernández or Gehring, Yamazaki, Schirra, and Cell Cycle Protocol fail to teach the present invention, the rejection based on them should be withdrawn.

Even if, assuming *arguendo*, the present invention is rendered *prima facie* obvious by the combination of Szyperski, Fernández or Gehring, Yamazaki, Schirra, and Cell Cycle Protocol, which it is not, such a *prima facie* case of obviousness is clearly rebutted by the present invention's satisfying a long-felt, but unfulfilled need (Szyperski Declaration ¶¶ 14-21).

Rapid resonance assignment is a prerequisite for rapid protein NMR structure determination and, thus, for high-throughput (HTP) structure determination and structural genomics (Szyperski Declaration ¶ 15). The aims of structural genomics have been to (i) explore the naturally occurring "protein fold space" and (ii) contribute to the characterization of function through the assignment of atomic-resolution three-dimensional (3D) structures to proteins (*Id.*). The ultimate goal is to provide one or more representative

3D structures for every structural domain family in nature (*Id.*). It is now generally acknowledged that NMR will play an important role in this endeavor (*Id.*). The resulting demand for HTP structure determination requires fast and automated NMR data collection and analysis protocols (*Id.*).

Two key objectives for NMR data collection can be identified (Szyperski Declaration ¶ 16). Firstly, the measurement time should be minimized so as to lower the cost per structure and relax the constraint that NMR samples need to be stable over long time periods (*Id.*). Secondly, automated analysis requires recording of a redundant set of NMR spectra each affording good resolution, while it is also desirable to keep the total number of spectra small to reduce complications due to interspectral variations of chemical shifts (*Id.*). This second objective can be addressed by maximizing the dimensionality of the spectra (*Id.*). However, the joint realization of the first and second objective is impeded by the large lower bounds for measurement times of four (or higher) dimensional NMR spectra arising from the independent sampling of three (or more) indirect dimensions (*Id.*).

"Sampling limited" and "sensitivity limited" data collection regimes can be distinguished, depending on whether the sampling of the indirect dimensions or the sensitivity of the multidimensional NMR experiments *per se* determines the minimally achievable measurement time (Szyperski Declaration ¶ 17). Because structure determinations rely on nearly complete shift assignments routinely obtained using $^{13}C,^{15}N,^{1}H$-triple-resonance (TR) NMR, the development of techniques that avoid the sampling limited regime has been an important challenge (*Id.*).

The fact that there had been a long-felt need for rapid and complete protein resonance assignment was recognized by those of ordinary skill in the art, as shown by a number of publications published in 2001 (Szyperski Declaration ¶ 18). For example, Heinemann et al., "High-Throughput Three-Dimensional Protein Structure Determination," *Current Opinion in Biotechnology* 12:348-354 (2001) stated the following:

> The NMR structure determination process in itself consists of a number of different time consuming steps, independent of sample preparation, which until recently could take up to several months or even years. Recording a data set took a minimum of six to eight weeks, and the assignment of resonance signals, including sidechain signals, required at least three to four weeks. Furthermore, the interpretation of the NOEs (nuclear Overhauser effects) observed in NOESY (NOE spectroscopy)-type spectra could take a couple of months, followed by one or two weeks of

> structure calculation. To achieve high-throughput, these times have to be significantly reduced (emphasis added).

*See id.* at 351 (Szyperski Declaration ¶ 18).

In another 2001 journal article, Prestegard et al., "Nuclear Magnetic Resonance in the Era of Structural Genomics," *Biochemistry* 40:8677-8685 (2001), Prestegard et al. noted the following:

> A more severe limitation was that the time required for NMR data acquisition and analysis is long, and sample preparation requires the use of isotopically labeled media ($^{15}$N- and $^{13}$C-labeled proteins). There have been enormous strides made in the efficient production of proteins through expression in *E. coli* (citation omitted), and new cell-free production techniques pioneered in Japan promise more latitude in produced proteins and incorporated labels (citation omitted). However, the 4-6 weeks of acquisition and subsequent months-long periods required for assignment and structure determination is still a major obstacle (citation omitted). This time scale is not compatible with structural genomics objectives that would require 100-200 structures per year from each of the seven NIH-sponsored pilot centers (citation omitted) (emphasis added).

*See id.* at 8680 (Szyperski Declaration ¶ 18). Thus, at the time the present invention was made, about 4 to 8 weeks of NMR instrument time per protein structure were considered to be a realistic estimate for ~1 mM protein samples with molecular weights up to 15 kDa and, as indicated by the above statements, there had clearly been a long-felt and unfulfilled need to achieve "rapid" and complete protein resonance assignment (Szyperski Declaration ¶ 18).

The failure to solve this long-felt need was, in part, due to the lack of appreciation of the present invention's potential to accomplish rapid and complete protein resonance assignment (Szyperski Declaration ¶ 19). Thus, despite the advantages of RD NMR in reducing sampling requirements and minimal measurement time and Dr. Szyperski's prior publications describing a number of specific RD NMR experiments, there had been a general lack of interest in the field in using RD NMR for rapid protein resonance assignment (*Id.*). This is well demonstrated by the attached Panel Summary for a grant proposal entitled "Reduced Dimensionality NMR Spectroscopy for Structural Genomics" that Dr. Szyperski submitted to the National Science Foundation (NSF) when he sought to have his initial work on the present invention funded (*Id.*). The Panel Summary, which was attached to a letter

sent by Acting Deputy Division Director Christopher Greer, Ph.D. on May 5, 2000, indicating that the grant proposal could not be supported, outlines the salient points raised in the panel discussion of Dr. Szyperski's proposal (*Id.*). It stated:

> The PI proposes to further develop methods to reduce the time for structure determination by NMR. This work is based on some nice experiments that the PI has already published. The PI projects that implementation of an RD NMR package would result in time savings for a facility trying to maximize throughput for protein NMR. Unfortunately, the project is essentially for the generation of software with no development of science. The NMR community has not appeared so far to be interested in RD. The panel concluded that new demonstrations of practicality of RD NMR were needed (emphasis added).

The subject matter of the present invention was published by, *inter alia*, Dr. Szyperski in Szyperski et al., "Reduced-Dimensionality NMR Spectroscopy For High-Throughput Protein Resonance Assignment," *Proc. Natl. Acad. Sci. USA* 99:8009-8014 (2002) (Szyperski Declaration ¶ 20). Comments from two reviewers for the journal were attached to the acceptance letter from the PNAS Office (*Id.*). In describing the aspects of the paper that are novel and important, Reviewer #II, stated:

> This paper describes the generalization of the concept of "reduced dimensionality" and its application to the NMR pulse sequences for protein resonance assignment. Efficiency in NMR data collection is one of the important concerns especially in structural genomics projects. This is not only a proposal of a concrete answer but also a proposal suggestive to other general problems (emphasis added).

(*Id.*). In addition, Reviewer #I noted the following:

> The reduced dimensionality experiments which are discussed in this paper are very important for enhancing information content to enable automated assignment of NMR resonances, and thereby high throughput structure determination by NMR. The concept of reduced dimensionality experiments is not new, but this manuscript puts together (for the first time to the knowledge of this reviewer) a suite of experiments. which are specifically useful for automated data analysis. The particular set of experiments seems to have been selected to be compatible with the AUTOASSIGN program from one of the authors, other sets may be optimal in

> other contexts but what is presented demonstrates the concept very well (emphasis added).

(*Id.*).

From these statements from referees in a high-quality journal such as the Proceedings of the National Academy of Sciences, it is apparent that the method of the present invention constitutes a significant advance in the art by having the capability to provide rapid and complete resonance assignment for high-throughput protein structure determination (Szyperski Declaration ¶ 21). The ability of this process to achieve such a long-felt, but unfulfilled need rebuts any *prima facie* obviousness. *See In re Dow Chemical*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

As further evidence of the unobviousness of the present invention, applicant submits that, at the time the present invention was made, there was considerable disbelief and skepticism in the field of NMR spectroscopy with regard to whether the present invention would be an effective method to use for rapid protein structure determination (Szyperski Declaration ¶ 22).

Structure determinations of proteins by NMR rely on the nearly complete assignment of chemical shifts, which can be obtained using multidimensional $^{13}C,^{15}N,^{1}H$-triple-resonance NMR methods (Szyperski Declaration ¶ 23). At the time Dr. Szyperski demonstrated rapid and complete backbone and side chain resonance assignments for the "Z domain" of *Staphylococcal* protein A by conducting a suite of RD $^{13}C,^{15}N,^{1}H$-triple-resonance NMR experiments, it was unknown whether conducting a suite of RD NMR experiments on a protein sample would be a sufficiently efficient method for rapid protein structure determination (*Id.*). Instead, there was prominent and prevalent concern that the added spectral overlap in the RD NMR spectra would render the use of RD NMR experiments ineffective in obtaining protein resonance assignments for structure determination (*Id.*). Thus, at the time the present invention was made, although the general concept of RD NMR had been previously published and would offer an attractive solution to reduce the minimal measurement times, no one had demonstrated obtaining "rapid" and complete resonance assignments for a protein by conducting a suite of RD NMR experiments (*Id.*). To the contrary, considerable skepticism existed in the field with regard to whether RD NMR would be an effective method to use for protein structure determination (*Id.*). Moreover, as already noted above, there had been a general lack of interest in the field in using RD NMR for rapid protein resonance assignment (*Id.*).

There were a number of reasons why no one believed that the present invention would be an effective method to use for protein structure determination (Szyperski Declaration ¶ 24). Firstly, NMR spectroscopy was relatively insensitive, which severely limited experimental design (*Id.*). Typically samples at ~1 mM protein concentration were required, preventing studies of proteins with very low solubility (*Id.*). Because of constraints on pulse sequence design arising from these sensitivity limitations, several different NMR spectra recorded over a four to six week period were necessary to obtain the information needed for a high-quality structure determination (*Id.*). These long data collection periods, in turn, put significant constraints on sample stability (*Id.*). Although multiple samples can be used in the structure determination process, each one must be stable for days to weeks with respect to precipitation, aggregation, and other forms of degradation (*Id.*). Secondly, manual analysis of these multiple NMR data sets was laborious and required significant expertise (*Id.*). Finally, in analyzing the NMR data, the density of constraints was sometimes inadequate for accurate structural analysis (*Id.*).

The considerable disbelief in the field regarding the present invention is demonstrated by the attached reviews of a grant proposal that Dr. Szyperski submitted to the NSF when he sought to have his initial work on the invention funded and by the attached reviews of a manuscript that he submitted to the Journal of American Chemical Society when he sought to have his work on the invention published (Szyperski Declaration ¶ 25). As the reviewers' comments reveal, both the reviewers of the NSF and the Journal of American Chemical Society shared strong skepticism that rapid and complete protein resonance assignment could be obtained by conducting a suite of RD NMR experiments and that the method of the present invention would work on larger size proteins (*Id.*). Nevertheless, Dr. Szyperski's NSF grant proposal was supported shortly after an initial rejection, while his manuscript, after being rejected by the Journal of American Chemical Society for containing subject matter too specialized for the general readers of the journal, was eventually published in a similar prestigious journal which has an even more generalized readership than the Journal of American Chemical Society (*Id.*). Furthermore, the initial view by experts in the field that the present invention would not be effective in determining the structure for larger size proteins was subsequently refuted by a number of publications co-authored by Dr. Szyperski (*Id.*).

After submitting a grant proposal entitled "CAREER: Reduced Dimensionality NMR Spectroscopy for Structural Genomics" to NSF, Dr. Szyperski received

a letter dated November 9, 1999, from Acting Deputy Division Director Jerry D. Cohen, Ph.D., initially indicating that the grant proposal could not be supported (Szyperski Declaration ¶ 26). Attached to that letter were reviews of the grant proposal by different reviewers and a Panel Summary (*Id.*). The Panel Summary stated:

> While recognizing that the PI pioneered the RD method in NMR, the panel believed that the PI must address important issues raised by the reviewers. In particular, the panel questioned whether the RD method will be broadly applicable, particularly to larger proteins with congested spectra. In addition, the PI should address the extent to which RD approaches truly reduce the main bottlenecks in NMR structure determination for high throughput structural genomics. The PI should address in more detail possible pitfalls in the proposed approaches and suggest alternatives.

(*Id.*). In particular, one of the reviewers stated:

> (1) It is not clear that this approach will benefit the structural genomics initiative. In proteins where spectral overlap is an issue, the introduction of more crosspeaks in the RD-NMR spectrum will pose a real limitation to the usefulness of this approach.

(*Id.*). A second reviewer, in discussing the subject matter of the proposal, noted the following:

> This CAREER proposal involves the development and application of reduced-dimensionality NMR to protein structure determination with the long-range goal of contributing to structural genomics. A focus will be on reducing the amount of NMR time required for resonance assignment and structure determination of proteins. Dr. Szyperski is one of the original developers of reduced dimensionality methodology when he was a postdoctoral in Wuethrich's [*sic*] lab and thus is uniquely qualified to carry out the proposed research program....The proposal is well written and the experiments are well outlined. An added strength of the proposal is the collaboration with Dr. Guy Montelione, where Dr. Montelione's AUTOASSIGN program will be use modified to incorporate the reduced dimensionality data. This is a potentially important simplification of the bottleneck in protein structure determination, the resonance assignments.

(*Id.*). A third reviewer noted the following:

> The PI has been the leader in the development of "reduced dimensionality" NMR experiments. In this approach, n chemical shifts are encoded into nû1 [*sic*] dimensions of a multidimensional NMR spectrum in order to maximize digital resolution while minimizing acquisition time.
>
> * * *
>
> I am most enthused about the proposed search for a robust minimum set of NMR experiments for structure determination of small protein domains and proteins. Defining such sets will be important for high throughput structure determination in structural genomics initiatives. The collaboration with Prof. Montelione also will enable the selected experiments to be integrated with the strengths of the AUTOASSIGN program. The proposal would be stronger if more discussion was presented of the criteria to be used in recognizing an appropriate set of experiments. How will the PI show that the designed set of experiments is generalizable (to proteins outside the test set) and robust (resistant to common experimental difficulties (poor resolution, disorder, etc.)?
>
> * * *
>
> The potential widespread application of the proposed methods in structural genomics provides the broad impact envisioned by the NSF's review criterion 2.

(*Id.*). A fourth reviewer stated:

> This application by Dr. Thomas A. Szyperski, proposes to develop approaches to more efficiently and more rapidly elucidate protein structures by using NMR techniques. The proposal addresses both fundamental research and applied research targeting the commercial efficiency of NMR groups focused on structural genomics initiatives.
>
> * * *
>
> Dr. Szyperski proposes to use a set of three proteins (ubiquitin, 8.6 kDa; RNaseA, 15 kDa; and Ns-1, 17 kDA). These three proteins are not representative of most proteins that will come from the genome. What about proteins in the 20 kDa to 30 kDa (or higher) where TROSY experiments promise to have the greatest impact in NMR, especially for its use in structural genomics? This has not been addressed. What are the limitations of his eventual protocol for using NMR in structural genomics programs.

(*Id.*). A fifth reviewer stated:

> 1) At the highest level, Dr. Szyperski needs to address if NMR is the proper method to participate in the process of structural genomics. This premise is just stated in the third line of the project summary and the third paragraph of the background section, but it is not supported by discussion at all. Can NMR really compete with X-ray for rapid turn over of structures? If so, on what subset of structures? What spectral properties are required?
> 2) Depending on the outcome of this question, the next issue should be a discussion of where the bottleneck for NMR structure determination lies.
> This reviewer is convinced that it does not lie with the resonance assignment at all. The most time consuming step by far is the NOE identification and iterative structure calculation and refinement. This holds for small proteins as well as large ones. There has even always been a upper size limit for which assignments could still be obtained, but no structure. Therefore, improvement of the efficiency of spectral assignment step does not really reduce the time necessary for structure determination and is therefore of very limited use to structural genomics.
> 3) At a third level, this reviewer differs strongly with Dr. Szyperski's assessment on the efficiency of reduced dimensionality experiments. The experiments are claimed to be more efficient than the current suite of existing experiments. This can be arguably be the case for very small proteins for which no overlap exists in the spectra. However, for the smallest of proteins there is no assignment problem at all, and new methods are not necessary either.
> The reduced dimensionality approach places more peaks in the NMR spectrum, which is always a bad idea when spectra get complicated. The next problem is that in experiments such as HNCAHA, there are two Ca frequencies per HN. Thus, the reduced dimensionality experiment will generate 4 peaks for these two peaks for which it is not known how they pair up. It gets worse if there is 2D HN degeneracy. Dr. Szyperski's solution (published by him in the past) to overcome this is to mistune the tau_4 delay in order to obtain axial peaks that contain the HNCA information. But, mistuning will negatively affect the sensitivity of the HNCAHA peaks. The next problem is that in order to obtain high resolution in N-1 dimensions, the indirect time-domain FIDs needs to be collected to high resolution. This leads to low sensitivity of the data. Also, the RD N-1 dimensional experiments cause a splitting of all peaks, which cause a reduction of sensitivity as compared to the N-dimensional experiment. At best, the sensitivity becomes equal if spectra get symmetrized around the center CA positions (which is different for every amino

> acid). As such, this reviewer is not really happy with the further development of the reduced dimensionality experiments.

(*Id.*).

Subsequent to the submission of the above career grant proposal, Dr. Szyperski submitted a significantly revised grant proposal entitled "Reduced Dimensionality NMR Spectroscopy for Structural Genomics" to NSF (Szyperski Declaration ¶ 27). On May 5, 2000, Acting Deputy Division Director Christopher Greer, Ph.D. sent Dr. Szyperski a letter (see Exhibit 5), indicating that the grant proposal could not be supported (*Id.*). Attached to that letter was a Panel Summary, as well as reviews of the proposal by different reviewers (*Id.*). In describing the significance of the proposed work, one of the reviewers stated:

> Criterion 1: Dr. Szyperski proposes further develop reduced dimensionality (RD) triple resonance NMR methods for use in structural genomics. The research will focus upon development of a protocol that will allow identification of minimal sets of NMR data for structure determination. These advances will be incorporated into automated structure determination schemes to further enhance applicability to a large number of protein targets. The major strengths of the proposal are the expertise of the P.I. in the general area and the importance of the time reductions which potentially could result from the work thereby facilitating determination of a large number of protein structures.
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> Criterion 2: The development of methods to facilitate the rapid solution of atomic resolution structures will have a profound impact on the area of structural genomics. Clearly, one of the limitations of structure determination with high-field NMR is the time required for data collection. The studies proposed hold the potential to significantly lessen this time constraint and to lead to the applicability of modern NMR methods to a larger number of proteins.

(*Id.*). A second reviewer noted the following:

> This is a very good - excellent proposal by a starting investigator who has made excellent contributions in the field of biomolecular NMR. The proposal is very sound and promises to greatly enhance the utility of solution NMR for structural genomics. For many of the proteins that are likely to be considered by NMR reduced

> dimensionality NMR is the way to go, offering savings in measuring time. Thus the development of a robust set of experiments is an important step. The applicant has made very important contributions in this area previously and he has the equipment, resources and expertise to continue. I recommend funding.

(*Id.*). A third reviewer stated:

> The PI has proposed an orchestrated approach for addressing one of the three major "bottle necks" in the use of high resolution NMR in structure-based genomics. He proposes the development of innovative and novel techniques that would reduce the total instrument time required for obtaining the data needed for sequential resonance assignments and structure determination for small to medium sized proteins. This work dovetails nicely into major research initiatives in the area of functional genomics that are being pursued both here in the US and elsewhere. The PI is superbly qualified and equipped for the proposed studies, with a strong publication record in this area and with ample computer facilities and NMR instrumentation at his disposal.
> The proposed studies would make important and relatively novel contributions to the field of structural genomics by developing techniques in two general areas. First, further development of reduced dimensionality (RD) experiments have the potential to dramatically reduce the time required for acquisition and improve the quality of multidimensional NMR experiments for rapid assignment and structure determination. Second, the development of techniques to combine the measurement of residual dipolar couplings with resonance assignment experiments, and to use the variations in residual dipolar couplings to resolve chemical shift degeneracy will further optimize the amount of information extracted from experimental data.
> Potential problems seem to be adequately addressed. The most obvious problem in the RD approach is of course the loss of spectral resolution. As the PI points out, the RD triple resonance techniques will benefit from incorporation of TROSY schemes, since the slowly relaxing component selected by TROSY yields a sharper resonance peak and will be of great value in optimizing spectral resolution. This should be adequate for the small to medium sized proteins to which the proposed techniques would be applied.

(*Id.*). A fourth reviewer noted the following:

This is a very good application of a talented scientist who recently joined the faculty of SUNY Buffalo. The proposed work is to utilize and further develop a principle called "reduced dimensionality" (RD) for reducing the measurement time of multidimensional NMR experiments. The PI developed the method while he was in the laboratory of Dr. Wuthrich in Zurich. The idea behind this approach is to record data in a way that both the sum and the difference of the frequencies of a pair of spins is measured along a single indirect dimension so that the information of two dimensions can be read in a single dimension. Thus, one can obtain the information of a 4D experiment essentially in the time one usually spends for a 3D experiment. In more recent implementation, Dr Szyperski has developed a way to also record the central peak (axial peak), which may provide additional useful information. The PI claims that this is particularly useful for applications in structural genomics where it is important to acquire spectral information as fast as possible. The proposal also proposes to use this methodology for measuring residual dipolar couplings in partially aligned systems. The PI describes convincingly that this information can be obtained from the central peaks in the more recent RD pulse sequences.
This is a technique-oriented proposal. The PI has first described the RD principle seven years ago. Several other groups have applied the technique although it hasn't yet found wide-spread use. However, the benefit of shorter measuring times claimed by the PI is obvious. The reason why the technique hasn't had wide impact may be that it requires additions and subtractions of peak positions to obtain chemical shift data, which complicates analysis of large data sets. This will be less of an issue if the experiments are incorporated in automated assignment routines. Thus, the proposed collaboration with the Montelione laboratory is a very positive aspect of this proposal. Another reason why the RD approach hasn't been used widely is that the primary limitation of NMR structure determination is still the process of making well-behaving protein samples. This may no more be a concern in a structural genomics effort where hopefully many well-behaving proteins will await there structures being solved. In this respect, the choice of ubiquitin and protein Z and other well-characterized proteins is a little distracting.
Overall, this is a very good application by a new investigator who is a highly talented NMR expert. The technology development proposed has potentially high impact for protein structure determination. The knowledge and research of the PI will have high educational impact on the local structural biology community.

(*Id.*). A fifth reviewer noted:

> This proposal focuses on expanding the role of high resolution NMR in a very important, and currently high profile, area of scientific activity, structural genomics. Hypothesis underlying this general area is that the wealth of information coming from sequencing projects can be tapped by solving sufficient numbers of protein structures quickly to provide examples from all fold families (several thousand). X-ray crystallography is clearly the major player in this area, but NMR is important because of its applicability to proteins that do not give diffraction quality crystals. One primary limitation of NMR is that data collection using conventional approaches is slow, requiring on the order of a month of spectrometer time for each protein to be solved. This proposal would expedite the process by identifying a minimal set of NMR experiments, basing these on reduced dimensionality experiments, exploring suitability for automated assignment, and extending schemes to measurement of residual dipolar couplings. The activity proposed is very useful and it would be carried out under the direction of an investigator with an excellent record. The reduced dimensionality trick, which relies on a proper collection of zero and two quantum coherences, is novel, and one pioneered by the investigator (although there are other examples using simultaneous evolution of two types of chemical shift to reduce dimensions). The proposed interaction with the Montelione group on incorporation of the reduced dimensionality experiments into the AUTOASSIGN program is excellent. And, the extension to collection of residual dipolar data could do much to improve the reliability of assignment and structure determination.

(*Id.*).

Despite the favorable and positive comments by the different reviewers as shown above, the grant proposal was rejected, as indicated by the May 5, 2000, letter from Christopher Greer, Ph.D mentioned above; however, shortly after, Thomas E. Smith, Ph.D. from the same Division mailed Dr. Szyperski a letter, informing him that his proposal would be supported (Szyperski Declaration ¶ 28).

Subsequently, Dr. Szyperski submitted a manuscript entitled "Reduced-dimensionality NMR Spectroscopy for High-Throughput Protein Resonance Assignment: Implementation and Automated Analysis" to the Journal of American Chemical Society to have his work on the invention published (Szyperski Declaration ¶ 29). On July 17, 2001, Associate Editor Dr. F. Ann Walker mailed Dr. Szyperski a letter, rejecting the manuscript for publication and attaching comments from two reviewers (*Id.*). In that letter, Dr. Walker stated that both of the reviewers feel that the work was appropriate for publication in the

Journal, but only after a number of major points were addressed (*Id.*). In particular, Reviewer 1 stated:

> This paper is largely a statement of advocacy rather than a critical scientific evaluation and account. While there is certainly merit in reduced dimensionality experiments for accelerating resonance assignments, the case study of a 4.5. ns correlation time polypeptide, the projected enhancements with cryoprobes, single transient spectra, etc. are not only misleading for the general scientific readership but scientifically indefensible with the data shown.
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> Thus, the paper would only be acceptable after major revision. This includes shortening the paper to remove much of the redundancy in statements and in clearly delineating the results from predictions.

(*Id.*). Reviewer 2, in discussing the subject matter of the manuscript, noted the following:

> The manuscript of Szyperski et al. presents a suite of reduced dimensionality triple resonance experiments for the rapid assignment of the backbone and side chain resonances of small to medium-sized proteins. A major part of the discussion deals with a critical comparison of the sensitivity of the individual experiments and the optimisation of measuring time taking into account the requirements of high spectral resolution and sufficient signal to noise. In addition, analysis of these NMR data has been implemented in the program package AutoAssign. Although I believe that the manuscript contains some interesting ideas, I am sceptical [*sic*] whether it merits (in the present form) publication in the Journal of the American Chemical Society .
>
> The authors present eight unpublished pulse sequences for triple resonance experiments using the so called reduced dimensionality approach. These experiments are well presented with a comprehensive description of the different pulse sequences in the Supporting Information. This part of the manuscript is certainly of interest to the biomolecular NMR community and merits publication in a specialised NMR journal.
>
> The major aim of the manuscript, however, is to present a new general strategy for speeding up the NMR assignment step of proteins. Reduced dimensionality experiments provide connectivities between four different nuclei and the high spectral resolution required for an automated data analysis. In addition, the authors present a comparison of the sensitivity of eleven NMR experiments recorded on a small protein of 63 residues at a

> magnetic field strength of 14.1 T, and discuss theses results in terms of "minimal required data set" and "minimal required experimental time". Although I believe that NMR assignments will greatly benefit from the use of reduced dimensionality experiments, I have some major concerns about the conclusions drawn from the experimental results. The conclusions about the relative sensitivity of the NMR experiments are certainly valid for other proteins with similar molecular weight (well below 100 residues) and studied under similar experimental conditions (temperature, magnetic field strength), but they will (as the authors agree on page 13) completely change for larger molecules (higher tumbling correlation times). Along the same lines, the chosen set of eleven triple resonance experiments may (or may not) be the best choice for assignment of a small protein, but other experiments will certainly yield much better results in the case of larger perdeuterated or randomly fractional deuterated proteins. Finally, a combination of reduced dimensionality experiments (for the most sensitive ones) and standard 3D triple resonance experiments (for the less sensitive ones) seems to me a better choice than the one presented in the manuscript. Thus the major conclusions of the manuscript are rather subjective and far from being general. By the way, the statement that complete NMR assignment of medium sized molecules will be possible "within a day or less" (page 19) is a very optimistic statement. It could even have a negative impact on most of the biomolecular NMR laboratories, where this step still requires a couple of weeks up to several months. This sentence should therefore be dropped from the manuscript unless the authors prove that they are really capable of what they are claiming.
>
> In conclusion, for the manuscript to be acceptable for publication in JACS, I suggest that the authors add at least one additional experimental study on a second test molecule (in the range of about 150 residues). This will help the work to be of more general interest to the readership of JACS. As recording of the NMR data sets and assignment can be accomplished in a couple of days by the authors, this requirement should not significantly delay publication of this work.

(*Id.*).

On August 8, 2001, Dr. Szyperski mailed a revised version of the manuscript to the Associate Editor of the Journal of American Chemical Society accompanied by a letter which responded to the reviewers' comments in detail (Szyperski Declaration ¶ 30). In responding to the reviewers' criticisms, Dr. Szyperski revised the manuscript to avoid claims beyond what was actually shown in the paper (*Id.*).

On August 13, 2001, the Associate Editor of the Journal of American Chemical Society sent Dr. Szyperski a letter, indicating that her journal remained unable to publish his manuscript due to the comments by Reviewer 1, to which his revised manuscript was sent (Szyperski Declaration ¶ 31). Reviewer 1 was of the view that the revised manuscript was not appropriate for publication in the journal, but rather should appear in a more specialized journal (*Id.*).

Dr. Szyperski soon after responded to the Associate Editor of the Journal of American Chemical Society, addressing each of the criticisms made by Reviewer 1 and pointing out the inappropriateness of all of the reviewer's points (Szyperski Declaration ¶ 32). In that letter, Dr. Szyperski asked whether it would be possible to receive the opinion of the Reviewer 2 on the revised manuscript (*Id.*).

On September 6, 2001, the Associate Editor of the Journal of American Chemical Society mailed Dr. Szyperski a letter, informing him that his manuscript was sent back to Reviewer 2, as well as a new reviewer who was an independent expert in the field, Reviewer 4, and, based on the reviewers' evaluations of the manuscript, concluding that the manuscript was not appropriate for publication in her journal (Szyperski Declaration ¶ 33). In particular, Reviewer 2 made the following comment:

> The revised manuscript of Szyperski et al. has significantly improved with respect to the original version by deleting much of the idealized projections to future achievements. This manuscript thus merits publication in a journal with a readership largely interested in the practical details of biomolecular NMR. The question remains whether it merits publication in the Journal of the American Chemical Society. Triple resonance experiments as well as reduced dimensionality spectroscopy are well known concepts widely used for the resonance assignment of proteins and nucleic acids. The detailed description of eleven RD triple-resonance experiments is certainly not of much interest to the broad readership of JACS. What would be of interest to many readers of JACS, especially molecular biologists interested in NMR as a tool to resolve structures, study molecular interfaces, etc., is the experimental proof that a certain set of NMR experiments combined with an automated assignment protocol will yield rapid assignment for a wide range of proteins. To achieve this goal, the proposed concept has to be applied to different (at least two or three) molecular systems in different molecular weight ranges and eventually using different isotope labels (e.g. partial deuteration). It is not sufficient to apply the method to a single small protein and add a reference to a couple of other proteins studied using the same

> strategy without providing any experimental evidence. By the way the spectrum of Fig. S20 also looks to me to correspond to a rather unstructured protein. Thus at the current state the proposed strategy is just one of many different possible strategies. I am actually using a different one based on another set of experiments, and neither me nor T. Szyperski and coworkers have proofed so far that their strategy is the more efficient one. The scientific content does not gain much by putting the work in the context of structural genomics. A valuable strategy to speed up the assignment process will be of interest to any NMR spectroscopist working on proteins not only those involved in structural genomics. On the other side the work would certainly benefit from a more thorough analysis of other time limiting factors like data processing, peak picking, and automated assignment.
> In agreement with Reviewer 1 I believe that the manuscript lacks sufficient experimental proof that the conclusions are valid for a large range of molecular systems, although some of the more specific points raised by Reviewer 1 can be argued to be rather subjective and of minor importance.
> In conclusion, I suggest that the major part of the manuscript containing the detailed analysis of the RD experiments and their application to the Z-domain should be published without significant changes in a more specialised NMR journal such as J. Biomol. NMR, and that the authors eventually resubmit at a later date a manuscript which discusses in more experimental detail their assignment strategy with respect to other methods for the example of representative protein systems without the need of a detailed description of NMR pulse sequences.

(*Id.*). Reviewer #4, noted the following:

> After reading the paper and associated correspondence, I agree with the Editor's decision. Both reviewers were initially of the opinion that the paper was not suitable for J.A.C.S., and the second review by Reviewer 1 reiterated this position. It seems to me that the points raised in the final correspondence from the author (disputing the Editor's decision) are not really the most important factors in the decision, but constitute more of a philosophical difference between the author and the reviewer. The main issue is that the subject of the paper is too specialized for the general readership of J.A.C.S. Publication in J.Biomol. NMR or even J.Magn.Reson. would be a much more appropriate option for this paper, since the target audience is actually a very small subset (those interested in rapid and automated NMR resonance assignments of proteins) of a small subset (those interested in NMR assignments of proteins) of a subset (those interested in biological NMR) of readers of J.A.C.S.

After the final rejection of his manuscript by the Journal of American Chemical Society, Dr. Szyperski submitted a substantially similar manuscript to the Proceedings of the National Academy of Sciences, which is as prestigious and has an even more generalized readership than JACS (Szyperski Declaration ¶ 34). On April 19, 2002, Dr. Szyperski received a letter from the PNAS Office, informing him that the PNAS Editorial Board accepted his manuscript for publication (*Id.*). Dr. Szyperski's published paper was cited in a recent article in the Journal of American Chemical Society by one of the leading research groups in the field, where the RD approach was hailed as being one of the most successful methods that have been proposed for rapid data collection (*Id.*). Subsequent work by Dr. Szyperski and his co-workers, where the same or substantially similar suite of RD NMR experiments was applied on different proteins of sizes ranging from 8 kDa to 21 kDa, was recognized and validated in additional papers published in Journal of Biomolecular NMR, Proteins, and Protein Science (*Id.*). For example, Szymczyna et al., "Letter to the Editor: $^{1}H$, $^{13}C$, and $^{15}N$ Resonance Assignments and Secondary Structure of the PWI Domain From SRm160 Using Reduced Dimensionality NMR, *J. Biomol. NMR* 22:299-300 (2002) shows that the total acquisition time for obtaining assignments of the protein backbone and side chain atoms for a 12.5 kDa polypeptide containing the PWI motif of SRm160 using a suite of RD NMR experiments was 44.5 hours (*Id.*).

The above-described series of events demonstrates that, at the time the present invention was made, there was substantial skepticism regarding whether it would be effective in obtaining rapid and complete resonance assignment for protein structure determination and whether it could be successfully applied to larger size proteins (Szyperski Declaration ¶ 35). The ability of the present invention to effectively obtain rapid and complete resonance assignment for protein structure determination and its successful application to larger size proteins, despite the belief by many in the art that the present invention could not achieve this result is a strong indicia of non-obviousness which further rebuts any *prima facie* case of obviousness established in the outstanding office action. Accordingly, the obviousness rejection in the outstanding office action should be withdrawn.

Finally, applicant hereby requests that the examiner consider the February 25, 2002, Supplemental Information Disclosure Statement, indicate such consideration by initialing the accompanying PTO-1449 form, and return the initialed PTO-1449 form with the next communication from the PTO.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: November 21, 2005

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